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Inhibiting LPAAT-β slows tumor growth in animal models

The LPAAT-β enzyme is part of the raf and mTOR pathways that activate tumor cell growth.

FRANKFURT – Drugs that inhibit an enzyme known as LPAAT-β may one day be part of a new generation of smart drugs. Researchers here at the 14th EORTC-NCI-AACR conference presented preclinical data showing the enzyme controls pathways key to cancer-cell survival.

Jack W. Singer, MD, the research program chairman of Cell Therapeutics said "the enzyme produces a cofactor for signaling pathways that may be essential to cancer cell growth and viability. Inhibition of this enzyme causes cancer cells to die."

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Singer said LPAAT-β could be a new cancer target for developing a new generation of smart drugs that specifically kill cancerous tissue while sparing normal tissue.

LPAAT-β belongs to a family of enzymes that catalyze the de novo biosynthesis of phosphatidic acid, a cofactor required for raf and mTOR activity. The enzyme is highly expressed in cancers of the lung, ovary, prostate, bladder, cervix and brain but is minimally expressed in most normal tissues.

When LPATT-β was overexpressed in cell lines, they became more tumorigenic. The change was reversed when the overexpressed gene was removed. Using a genetic technique known as RNAi to decrease LPAAT-β expression, researchers were able to decrease the proliferation of tumor cells.

Researchers also developed small molecule inhibitors specific to the enzyme. These compounds were able to induce apoptosis in a wide variety of tumor cell lines.

One of these compounds, CT-32228 (CTI), was used in nude mice bearing HT-29 colon cancer. Treatment was nontoxic and significantly delayed tumor growth. Similar results were seen with related compounds in mice with Lewis lung cancers or NCI-H460 human lung cancers.

The enzyme "potentially represents a novel and selective target for cancer therapy that can be inhibited by low molecular weight drug-like compounds," Singer said. **H/Ot**

For more information:

Singer JW, et al. CT-32228, a specific inhibitor of lysophosphatidic acid acetyltransferase-beta (LPAAT-beta) causes selective tumor cell apoptosis. Abstract #215. Presented at the 14th EORTC-NCI-AACR Conference. Nov. 19-22, 2002. Frankfurt.